Ventriculomegaly, Intrauterine Growth Restriction, and Congenital Heart Defects as Salient Prenatal Sonographic Findings of Miller-Dieker Lissencephaly Syndrome Associated With Monosomy 17p (17p13.2 → pter) in a Fetus

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SUMMARY

Objective: To present the prenatal sonographic findings of Miller-Dieker lissencephaly syndrome (MDLS) associated with monosomy 17p (17p13.2 → pter) in a fetus.

Case Report: A 25-year-old, gravida 3, para 1, woman was referred to Mackay Memorial Hospital at 36 weeks' gestation because of ventriculomegaly, intrauterine growth restriction, and congenital heart defects detected by ultrasound. The pregnancy was uneventful until 32 weeks of gestation when ventriculomegaly was first noted. Level II ultrasound at 36 weeks' gestation showed a fetal biometry equivalent to 32 weeks, tetralogy of Fallot, and bilateral ventriculomegaly. At 38 weeks' gestation, a 2,308-g female baby was delivered with facial dysmorphism. A presumptive diagnosis of DiGeorge syndrome was made. However, no del22q11 could be detected by rapid fluorescence *in situ* hybridization analysis. Cytogenetic analysis of the cord blood revealed a 46,XX,del(17)(p13.2) karyotype. Brain ultrasound showed paucity of gyral and sulcal development. Computed tomography scans showed tetralogy of Fallot. Magnetic resonance imaging of the brain showed lissencephaly and colpocephaly. The final diagnosis was MDLS.

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Conclusion: Ventriculomegaly and intrauterine growth restriction are important prenatal ultrasound markers of MDLS. Prenatal diagnosis of conotruncal heart defects in association with ventriculomegaly and intrauterine growth restriction should include a detailed investigation of MDLS in addition to DiGeorge syndrome. [*Taiwan J Obstet Gynecol* 2010;49(1):81–86]

Key Words: congenital heart defects, intrauterine growth restriction, lissencephaly, Miller-Dieker syndrome, monosomy 17p, ventriculomegaly

Introduction

Miller-Dieker lissencephaly syndrome (MDLS; OMIM 247200) is characterized by microcephaly, lissencephaly (a smooth brain without convolutions or gyri), and a distinctive facial appearance of prominent forehead, bitemporal hollowing, a short nose with upturned nares, a protuberant upper lip, and a small jaw. MDLS is an autosomal dominant disorder and can be caused by deletions or mutations of the *LIS1* gene (*PAFAH1B1*; OMIM 601545) on 17p13.3 [1]. Deletions of the additional genes, such as *14-3-3ε* and *CRK*, in combination with deletions of *LIS1* may contribute to the more severe form of lissencephaly seen only in patients with MDLS [2]. The incomplete development of the brain causes severe mental deficiency with initial hypotonia, opisthotonos, spasticity, and seizures in patients with MDLS [3]. Other central nervous system abnormalities associated with MDLS include absent or hypoplastic corpus callosum, large cavum septi pellucidi, and small midline calcifications in the region of the third ventricle [3]. MDLS may be associated with polyhydramnios, omphalocele [4], and neural tube defects [5]. Other occasional abnormalities include tetralogy of Fallot, ventricular septal defect (VSD), valvular pulmonary stenosis, intrauterine growth restriction (IUGR), decreased fetal activity, cystic dysplasia of the kidney, cleft palate, and cataract [3]. Here, we report a fetus with MDLS and monosomy 17p (17p13.2 → pter), presenting ventriculomegaly, IUGR, and congenital heart defects as salient prenatal sonographic findings in the third trimester.

Case Report

A 25-year-old, gravida 3, para 1, woman was referred to Mackay Memorial Hospital at 36 weeks' gestation because of ventriculomegaly, IUGR, and congenital heart defects on ultrasound. The woman and her husband were non-consanguineous and healthy, and there was no family history of congenital heart defects or central nervous system abnormalities. The woman had a healthy 5-year-old son and had experienced one spontaneous abortion. She did not have diabetes mellitus and denied any exposure to teratogenic agents or infectious diseases during this pregnancy. The pregnancy was uneventful until 32 weeks' gestation when ventriculomegaly was first noted on prenatal ultrasound. Genetic analysis was suggested but was declined. Level II ultrasound examination at 36 weeks' gestation revealed a singleton fetus with a biparietal diameter, an abdominal circumference equivalent to 32 weeks, a femur length equivalent to 30 weeks, atrial septal defect, VSD, tetralogy of Fallot, and bilateral ventriculomegaly with the width of the lateral ventricular atria > 12 mm (Figure 1). Brain ultrasound findings were otherwise unremarkable, and the amniotic fluid volume was normal. At 38 weeks of gestation, a 2,308-g female baby, with a small head, wrinkling of the forehead, a broad nasal bridge, anteverted nares, epicanthal folds, micrognathia, a long thin upper lip and low-set ears, was delivered. The body length was 46 cm (< 5th centile), and the head circumference was 31 cm (< 5th centile). A presumptive diagnosis of DiGeorge syndrome was made. However, no del22q11 could be detected in the cord blood by fluorescence *in situ* hybridization, and cytogenetic analysis of the cord blood revealed a

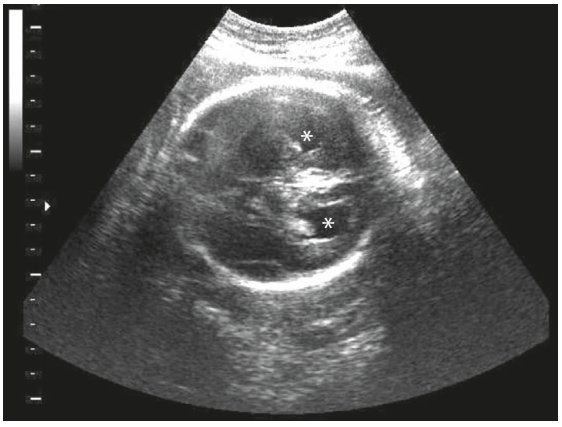

Figure 1. Prenatal ultrasound at 36 weeks' gestation showing bilateral ventriculomegaly (*) with the width of the lateral ventricular atria measuring 15 mm.

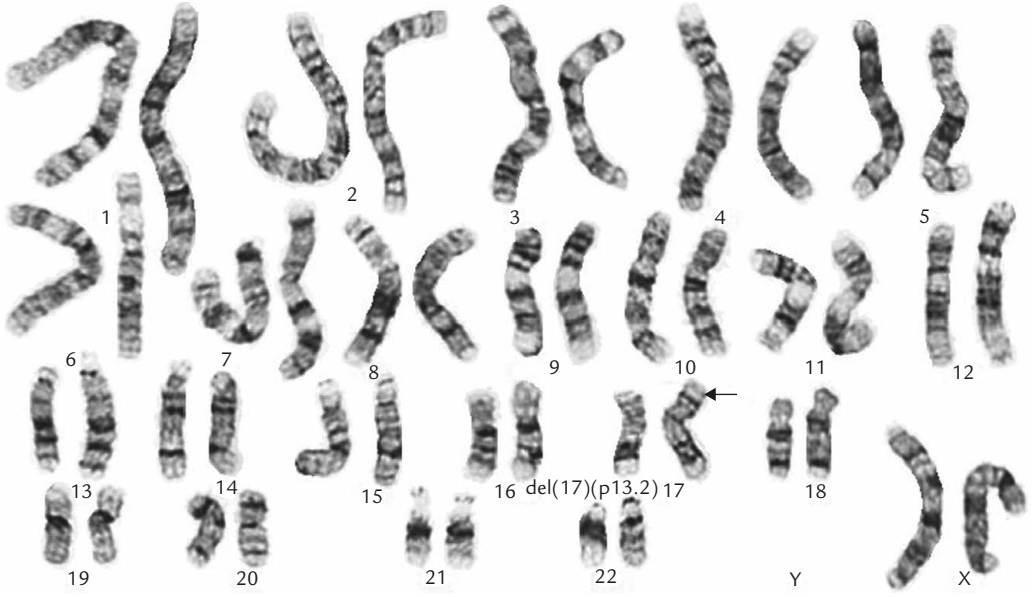

Figure 2. A 46,XX,del(17)(p13.2) karyotype. The arrow indicates the breakpoint.

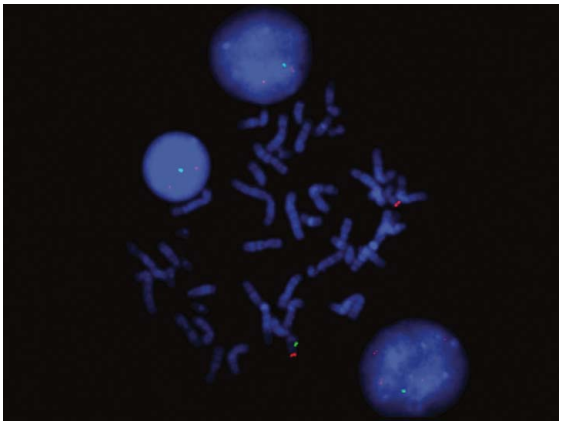

Figure 3. Fluorescence *in situ* hybridization analysis using the 17p13.3-specific probe RP11-74E22 (2474720-2652130 bp; spectrum green) and the 17q25.3 control probe RP11-304E2 (spectrum red) showed absence of one green signal indicating a heterozygous deletion of the *LIS1* gene (2443673-2535659 bp).

46,XX,del(17)(p13.2) karyotype (Figure 2). Fluorescence *in situ* hybridization, analysis using an informative 17p13.3 DNA probe showed haploinsufficiency of the *LIS1* gene (Figure 3). Parental karyotypes were normal. Echocardiography showed atrial septal defect, VSD, patent ductus arteriosus, aortic regurgitation, and pulmonary valve atresia. Computed tomography scans showed tetralogy of Fallot with VSD, patent ductus arteriosus, right ventricle outflow tract hypoplasia, and overriding aorta (Figure 4). Brain ultrasound showed paucity of gyral and sulcal development and enlargement of the temporal horns of bilateral ventricles, suggestive of lissencephaly. Magnetic resonance imaging (MRI) of the brain showed lissencephaly with agyria/pachygyria, agenesis of the corpus callosum, and ventricular dilation (Figure 5). A diagnosis of MDLS was made. At the age of 18 months, the infant had suffered from growth retardation, developmental delay, and seizures.

Discussion

Type I or classic lissencephaly is caused by abnormal neuronal migration and failure of the brain neurons to reach the cortical plate at 9–13 weeks of gestation. Classic lissencephaly is characterized by a spectrum of agyria, mixed agyria/pachygyria, and pachygyria in association with an abnormally thick and poorly organized cortex, with four primitive layers instead of the normal six cortical layers, diffuse neuronal heterotopia, ventricular dilation, and hypoplastic corpus callosum. Classic lissencephaly includes lissencephaly 1 (LIS1; OMIM 607432), lissencephaly 2 (LIS2; OMIM 257320), lissencephaly 3 (LIS3; OMIM 611603), lissencephaly, X-linked, 1 (LISX1; OMIM 300067) and lissencephaly, X-linked, 2 (LISX2; OMIM 300215) [6, 7]. LIS1 includes classic lissencephaly, subcortical laminar heterotopia, subcortical band heterotopia (SBH), and isolated lissencephaly sequence (ILS). LIS1 can be caused by mutations in the *PAFAH1B1* (*LIS1*) gene (OMIM 601545; gene map locus 17p13.3). MDLS is classic lissencephaly in association with facial abnormalities and other major abnormalities, whereas X-linked lissencephaly and ILS are rarely associated with other major abnormalities. Subcortical laminar heterotopia, SBH, and ILS are the less severe forms of classic lissencephaly. LIS2 or

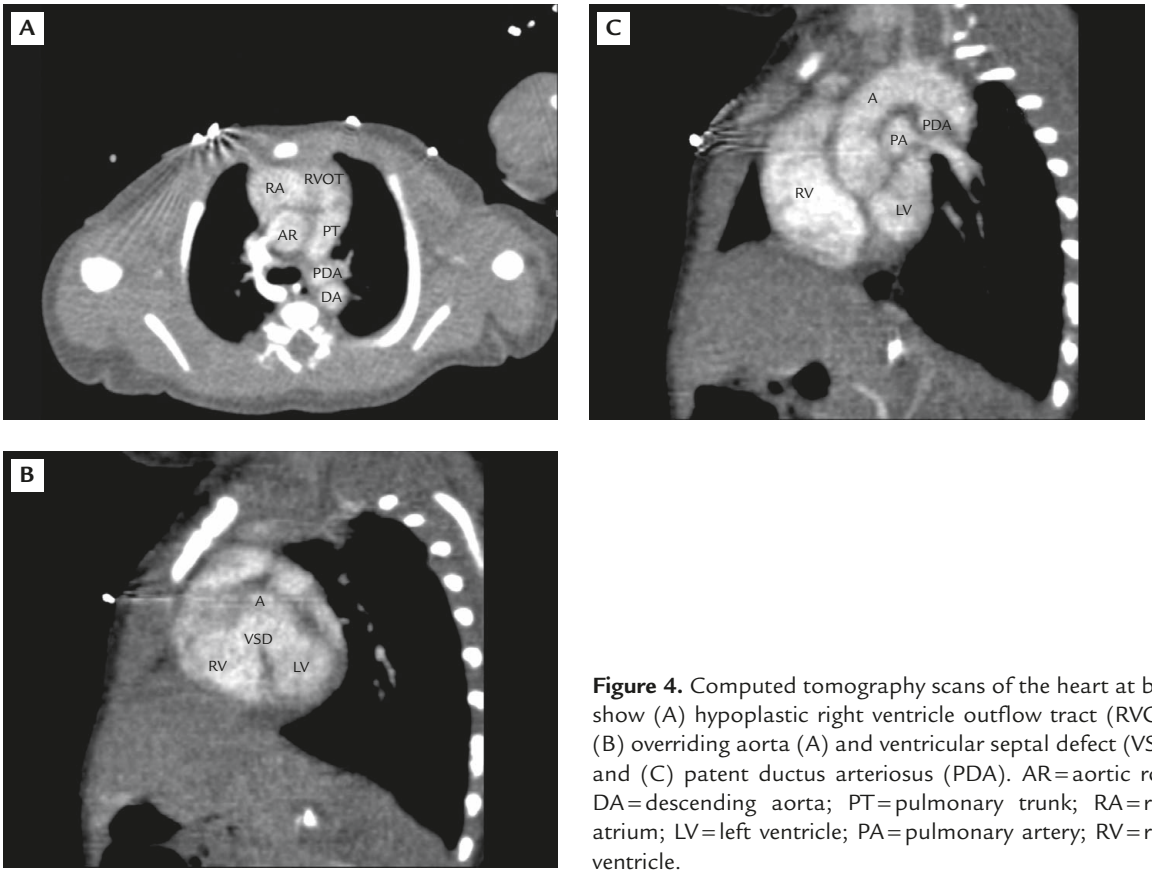

Figure 4. Computed tomography scans of the heart at birth show (A) hypoplastic right ventricle outflow tract (RVOT); (B) overriding aorta (A) and ventricular septal defect (VSD); and (C) patent ductus arteriosus (PDA). AR=aortic root; DA=descending aorta; PT=pulmonary trunk; RA=right atrium; LV=left ventricle; PA=pulmonary artery; RV=right ventricle.

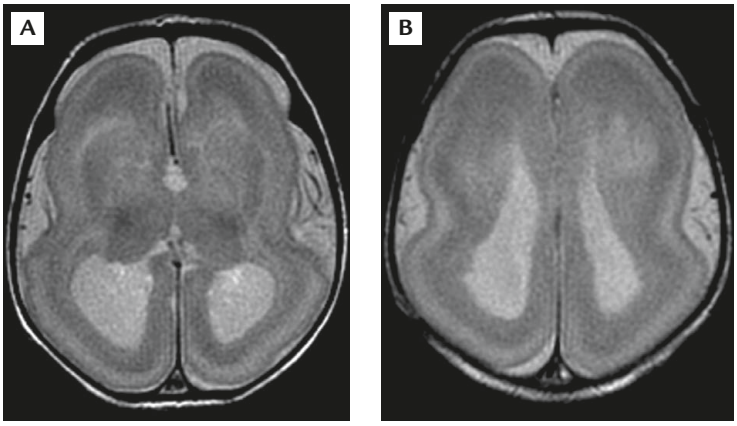

Figure 5. (A, B) Magnetic resonance imaging of the brain at birth shows agyria/pachygyria, a figure-of-eight appearance of the brain, a wide and shallow sylvian fissure, dilation of the lateral ventricles, and agenesis of the corpus callosum.

Norman-Roberts syndrome can be caused by mutations in the *RELN* gene (OMIM 600514; gene map locus 7q22). LIS3 can be caused by mutations in the *TUBA1A* gene (OMIM 602529; gene map locus 12q12-q14). LISX1 includes lissencephaly and agenesis of the corpus callosum, X-linked subcortical laminar heterotopia, X-linked SBH and double cortex syndrome, and can be caused by mutations in the *DCX* gene (OMIM 300121; gene map locus Xq22.3-q23). LISX2 includes X-linked lissencephaly with ambiguous genitalia, and hydranencephaly and abnormal genitalia, and can be caused by mutations in the *ARX* gene (OMIM 300382; gene map locus Xp22.13).

Type II or cobblestone lissencephaly is characterized by a disorganized unlayered cortex, overmigration of neurons into the subpial space and gliovascular proliferation. The term *cobblestone* is applied because of a granular surface and effacement of gyri owing to ectopic neurons with gliovascular proliferation near the surface of the cortex showing a bumpy cobblestone-like

appearance [7]. Type II lissencephaly can be observed in four prototypic autosomal recessive disorders: Walker-Warburg syndrome, Fukuyama-type congenital muscular dystrophy, muscle-eye-brain disease and muscular dystrophy, and type IC congenital muscular dystrophy [6,7]. Walker-Warburg syndrome (OMIM 236670) or HARD±E syndrome is an autosomal recessive disorder characterized by hydrocephalus (H), agyria (A), retinal dysplasia (RD) with or without encephalocele (±E), and congenital muscular dystrophy. Brain abnormalities associated with Walker-Warburg syndrome include type II lissencephaly (100%), cerebellar malformation (100%), ventriculomegaly (95%), Dandy-Walker malformation (53%), and occipital encephalocele (24%) [8]. Walker-Warburg syndrome can be caused by mutations in the genes of *POMT1* (OMIM 607423), *FKTN* (OMIM 607440), *FKRP* (OMIM 606596), *POMT2* (OMIM 607439), and *LARGE* (OMIM 603590). Fukuyama-type congenital muscular dystrophy (OMIM 253800) has an overlapping phenotype with mild Walker-Warburg syndrome and can be caused by mutations in the *FKTN* gene (OMIM 607440) encoding fukutin. Muscular dystrophy, congenital, type IC (MDC1C; OMIM 606612), is an autosomal recessive disorder characterized by muscle weakness and structural brain defects, and can be caused by mutations in the *FKRP* gene. Muscle-eye-brain disease (OMIM 253280) is an autosomal recessive disorder that has phenotypic similarities with Walker-Warburg syndrome, and can be caused by mutations in the *FKRP* gene and the *POMGNT1* gene (OMIM 606822).

Prenatal ultrasound in the present case revealed ventriculomegaly, IUGR, and congenital heart defects in the third trimester. In fetuses with MDLS, common sonographic findings include widespread agyria, abnormal sylvian fissure and insula, ventriculomegaly (usually mild), corpus callosum dysgenesis, microcephaly, IUGR and polyhydramnios, and less common findings include micrognathia, congenital heart defects, genitourinary anomalies, and omphalocele [6,9].

Ventriculomegaly has been shown to be an important and common prenatal ultrasound marker of MDLS [6,9,10]. Greco et al [11] reported a case of isolated lissencephaly diagnosed by fetal MRI, and cerebral ventriculomegaly at 24 weeks' gestation was the presumptive diagnosis on prenatal ultrasound. Fong et al [9] found that six of seven fetuses with MDLS manifested ventriculomegaly. Pastorino et al [10] reported borderline ventriculomegaly of the lateral cerebral ventricles at 35 weeks' gestation as the main presenting feature of lissencephaly in a fetus. In this case, the fetal brain surface appeared smooth, and a fetal brain MRI revealed lissencephaly. Lenzini et al [12] reported a fetus with an apparently balanced 46,*XX*,t(17;18)(p13;p11.2) karyotype but a 4-Mb microdeletion at 17p13.3, with the prenatal sonographic findings of polyhydramnios, IUGR, microcephaly, ventriculomegaly, dysgenetic corpus callosum, hypoechogenic cerebral parenchyma, pachygyria, talipes equinovarus, and hyperechoic renal parenchyma at 29 weeks of gestation. Lin et al [13] reported polyhydramnios, IUGR and ventriculomegaly at 31 weeks' gestation in a fetus with monosomy 17p (17p13.3 → pter) and MDLS. Fong et al [9] suggested that mild ventriculomegaly can be the first sign of abnormal/delayed brain maturation, and in fetuses with apparently isolated mild ventriculomegaly, routine sonographic examination of cerebral sulci at 24–26 weeks of gestation should be performed, and both MRI and fluorescence *in situ* hybridization for 17p13.3 deletion should be performed if there is abnormal sulcal development. Fetal cerebral sulci can be sonographically demonstrated as early as 18 weeks' gestation and by 30–32 weeks, most of the main sulci can be demonstrated [14–16]. However, there is a mean lag of 2 or more weeks in the development of sulci/fissures in ventriculomegaly, and ventriculomegaly may obscure visualization of the sulcal pattern. Only severe forms of lissencephaly, such as agyria, can be detected on prenatal ultrasound, and milder forms of pachygyria and SBH are difficult to diagnose [6,9,17].

Extracranial abnormalities, such as IUGR, congenital heart defects and omphalocele, may be associated with MDLS on prenatal ultrasound. IUGR has been a common finding associated with MDLS [3,6]. In a study of seven fetuses having MDLS, Fong et al [9] found that five had extracranial abnormalities including IUGR ($n=3$), micrognathia ($n=1$), and omphalocele ($n=1$). IUGR and renal abnormalities were found in the case of MDLS with monosomy 17p (17p13 → pter) reported by Lenzini et al [12]. Herman and Siegel [18] reported an MDLS fetus with severe IUGR, polyhydramnios, and a distal deletion of 17p. Tetralogy of Fallot has been an occasional finding associated with MDLS [3,6]. Saltzman et al [19] reported an MDLS fetus with a deletion of 17p13.3, IUGR, tetralogy of Fallot, severe polyhydramnios, and abnormal gyri at 31 weeks' gestation. Greenberg et al [20] reported a fetus with a deletion of 17p13, IUGR, double-outlet right ventricle, thymic hypoplasia and polyhydramnios, suggestive of DiGeorge syndrome. In fact, the present case was initially diagnosed as DiGeorge syndrome. Omphalocele can be a prenatally identifiable anomaly associated with MDLS [21–23]. Sermer et al [21] reported a case of 17p deletion associated with prenatally detected omphalocele, cardiomegaly, and

neural tube defect. Alvarado et al [22] reported MDLS and omphalocele in a family with multiple affected offspring with monosomy 17p (17p13.3 → pter) and a 46,XY,der(17)t(17;19)(p13.3;q13.33)pat karyotype. Chitayat et al [23] reported the prenatal diagnosis of omphalocele and mild cerebral ventriculomegaly in a patient with MDLS and a deletion of 17p13.3.

In conclusion, we have presented a case in which the features of MDLS and monosomy 17p (17p13.2 → pter) were present. We suggest that prenatal diagnosis of conotruncal heart defects in association with ventriculomegaly and IUGR should include a detailed investigation of MDLS in addition to DiGeorge syndrome.

Acknowledgments

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